

THE SYNDROME OF EXCESSIVE THYROCALCITONIN PRODUCED BY MEDULLARY CARCINOMA OF THE THYROID*

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The association of medullary carcinoma of the thyroid with pheochromocytoma and other neuroectodermal tumors constitutes a now well-recognized clinical syndrome.¹⁻⁶ In several cases^{3, 7-10} adenomas or hyperplasia of the parathyroid glands has been noted. Williams¹¹ has presented evidence to suggest that the tumors in the thyroid gland may arise from parafollicular cells, which in most mammals are considered to be the source of thyrocalcitonin,¹²⁻¹⁴ a hormone which lowers plasma calcium by inhibiting bone resorption.¹⁵

No syndrome in man resulting from hypersecretion of thyrocalcitonin has yet been documented conclusively. Two cases of so-called "calcitonin-excess syndrome" have been reported,^{16, 17} but hypocalcemia improved only briefly after total thyroidectomy.

The present case is the first documented example of a thyrocalcitonin-secreting tumor and of hypocalcemia with secondary hyperparathyroidism resulting from increased levels of circulating thyrocalcitonin.

Clinical Details.—Case report: A 32-year-old white male presented with a clinical picture typical of pheochromocytoma. Eleven years previously he had undergone subtotal thyroidectomy for carcinoma of the thyroid. Histological sections from that operation showed medullary carcinoma with abundant amyloid and calcification. Mild tetany postoperatively was readily controlled with calciferol and calcium supplements. These medications were stopped after 4 weeks without recurrence of tetany until 9 years later.

The patient's mother had died in her thirties of thyroid cancer, and his sister underwent thyroidectomy at the age of 17 for "adenocarcinoma" of the thyroid, from which she died 4 years later.

For 9 years after the thyroidectomy, the patient remained in excellent health. In 1965 he first developed diarrhea with occasional episodes of tetany. The symptoms were not sufficiently severe to interfere with his work as a dental technician. In February 1967, the diarrhea and tetany occurred more frequently and hypocalcemia was confirmed. Treatment was started with calciferol, 100,000 units daily; calcium lactate; and thyroid U.S.P., 120 mg daily. Thereafter he remained reasonably well until the onset of his present illness.

On admission he appeared gravely ill, with a labile blood pressure, paroxysmal tachycardia, and episodes of profuse sweating and extreme pallor. Chvostek's and Trousseau's signs were strongly positive. A clinical diagnosis was made of familial medullary carcinoma of the thyroid with pheochromocytoma and hypocalcemia. Treatment with calciferol was increased to 200,000 units daily, and total elemental calcium supplements to 3.35 gm daily.

Laboratory data showed: serum Ca 6.4 mg %, phosphate 3.0 mg %, alkaline phosphatase 8.8 Bodansky units; blood urea nitrogen 13 mg %, total plasma protein 6.5 gm %, normal serum electrolytes; protein-bound iodine 9.2 μ g %, total iodine 12.0 μ g %, thyroxine iodine 2.3 μ g % (normal 2.5-7.0/ μ g %); urinary vanilmandelic acid 80 mg/24 hr (normal 1.5-8.0), catecholamines unrecordably high, 5-hydroxyindoleacetic acid 3.5 mg/24 hr (normal 2-10). Electrocardiogram showed a wandering pacemaker

and frequent nodal rhythm. Adrenal arteriogram showed a tumor in the region of the left adrenal gland. Radiological survey showed no evidence of bone disease. Bone density did not appear to be either increased or decreased. There were no radiological features of osteoporosis, osteomalacia, or hyperparathyroidism.

At operation, bilateral pheochromocytomas were removed. Histologically these tumors were benign. The liver was extensively infiltrated by metastatic tissue, some of which was excised for thyrocalcitonin assay.

Calcium kinetics and balance studies: Combined radiocalcium and calcium balance studies were carried out 3 weeks postoperatively. Studies were performed while the patient was taking the following medications daily: calciferol 200,000 units, calcium gluconogalactogluconate (3.35 gm Ca), prednisone 10 mg, and thyroid U.S.P. 180 mg. The balance diet contained 1.58 gm calcium daily. Stable calcium estimations were by the method of ethylenediaminetetraacetate titration. Coinciding with the opening of the first balance period, the patient received 15 μ c of Ca^{47} intravenously (i.v.). Serum and urine specific activities were measured daily for 12 days; cumulative fecal isotope excretion was determined in three 4-day fecal pools. Methods of analyses and isotope measurements have been described elsewhere.¹⁸

Kinetic calculations were made after the method described by North *et al.*¹⁹ using an open-ended, single-compartment model.

Calcium infusion: The patient fasted overnight before the test and until after completion of the infusion. The infusion (calcium gluconate, 15 mg Ca/kg body weight, in 500 ml of 0.9% saline) was infused i.v. at a constant rate over 4 hr. Blood samples were taken at 0, 4, 6, 8, 12, and 24 hr after the start of the infusion.

Biological assay for thyrocalcitonin: The tumor removed from the liver was handled with special precautions, to minimize the possibility that thyrocalcitonin would be degraded before assay. The tissue was frozen within minutes after excision and extracted in 0.1 N HCl (10 ml/gm fresh tissue) by the same methods previously described in detail.²⁰ The extract was assayed biologically for thyrocalcitonin using 100–120-gm male rats (Holtzman Rat Co.) fed a low-calcium diet for one day.²¹

Peripheral venous plasma was also assayed biologically for thyrocalcitonin. HCl (0.1 ml of 0.1 N/1.5 ml plasma) was added just prior to assay, and the samples were injected in the assay rats subcutaneously, using the same methods as described for tumor extracts.

Radioimmunoassay for parathyroid hormone: Parathyroid hormone was measured in unextracted peripheral venous plasma by radioimmunoassay.²² Samples were tested at multiple dilutions in four separate assays. Two standard curves were used in each immunoassay, one curve with unlabeled bovine hormone, and a second curve with a partially purified, biologically standardized extract of human parathyroid hormone.²²

Results.—The experiments reported here were performed to gain insight into the mechanisms underlying this patient's hypocalcemia. Attention was focused first on the metastatic tumor in the liver. Histologically this was medullary carcinoma of the thyroid. An extract of the tumor produced significant hypocalcemia in the assay rats at a dose level of 0.25 μ l per rat (Fig. 1). Similar extracts of normal human thyroid glands must be administered at dose levels of 0.5–2.0 ml per rat to obtain hypocalcemic responses.²³ The potency of this tumor extract was 143 ± 1.32 MRC units/gm fresh weight—well over 1,000 times as potent as similar extracts of normal human thyroid tissue. (The factor following the symbol \times , when multiplied by and divided into the potency estimate, gives the standard error limits of the estimate.)

It has not previously been possible to detect thyrocalcitonin in peripheral human plasma by biological assay in rats. As shown in Table 1, however, this patient's plasma produced a profound hypocalcemic effect in the assay rats. The effect was greater when the patient was normocalcemic (postoperatively) than

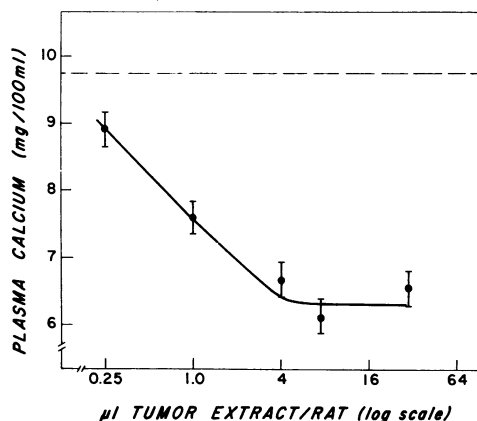


FIG. 1.—Hypocalcemic effect of the extract of the metastatic medullary carcinoma of the thyroid. The tumor was extracted with 10 ml of solvent/gm of fresh tissue, therefore each μ l of extract was equivalent to 100 μ g of tissue. Each point gives the mean value for four rats. The vertical lines give the standard error. The dashed horizontal line shows the mean plasma calcium level of control rats injected with solvent alone. Control extracts prepared from normal human tissues other than thyroid produced no hypocalcemic response in the assay rats.

preoperatively when he was severely hypocalcemic. Likewise, following an infusion of calcium the hypocalcemic activity in plasma increased fourfold. We presume that the hypocalcemic activity in the plasma represents thyrocalcitonin, and although it was probably being secreted constantly at a high rate by the tumor, secretion was stimulated even further by raising the plasma calcium level.

To rule out the possibility that the patient's hypocalcemia was due to hypoparathyroidism, plasma was taken when the patient was hypocalcemic and it was assayed for parathyroid hormone. The mean level found was 15 mU/ml,

TABLE 1. Bioassay of hypocalcemic activity in plasma.

Treatment		Plasma Calcium (mg/100 ml) ^a	
		Expt. 1	Expt. 2
Control solution ^b		9.5	10.1
MRC Res. Std. A	5 mU/rat	Nt ^c	9.4
MRC Res. Std. A	20 mU/rat	Nt	7.7
Normal human plasma	1.5 ml/rat	9.5	Nt
Normal human plasma	0.16 ml/rat	Nt	9.8
Patient's plasma, preop. ^d	1.5 ml/rat	8.4	Nt
Patient's plasma, postop. ^e	1.5 ml/rat	6.2	Nt
Patient's plasma, postop. ^e	0.16 ml/rat	Nt	8.1 ^g
Patient's plasma, postop. ^e	0.04 ml/rat	Nt	10.1
Patient's plasma, ^f preinfusion	0.2 ml/rat	Nt	8.9 ^h
Patient's plasma, ^f postinfusion	0.2 ml/rat	Nt	7.2 ⁱ

^a Mean values, 3 or 4 rats/group. The standard errors were 0.22–0.31 and 0.20–0.23 for expts. 1 and 2, respectively.

^b Tris buffer, 0.1M, pH 7.5 or 0.01 N HCl containing bovine serum albumin in (1 mg/ml). MRC Res. Std., Medical Research Council Research Standard.

^c Nt = not tested.

^d The serum calcium was 6.0–6.5 mg/100 ml at this time.

^e The serum calcium was 7.1 mg/100 ml at this time.

^f Samples obtained just prior to calcium infusion (serum calcium was 7.6 mg/100 ml) and 8 hr after the cessation of infusion (serum calcium was 11.0 mg/100 ml).

^g Equivalent to 95×1.29 MRC mU/ml. Approximately tenfold more hypocalcemic activity than the preoperative sample.

^h Equivalent to 39×1.27 MRC mU/ml.

ⁱ Equivalent to 159×1.40 MRC mU/ml.

a value well above the range of normal for the method (indeterminantly low levels to 4 mU/ml).

The findings of extraordinarily high concentrations of thyrocalcitonin in the metastatic tumor and in the plasma were interpreted as indicating synthesis of thyrocalcitonin by the tumor and its secretion into plasma. The resulting hypocalcemia acted to stimulate parathyroid hormone secretion to a level considerably above normal, but still inadequate to overcome the effect of the extremely high circulating concentration of thyrocalcitonin.²⁴ Results of kinetic measurements have been expressed in both plasma units and in mg calcium/kg body weight (Table 2). The former method of expression relates to movements of isotope only, and does not take into account the level of the serum calcium. Translated into mg calcium/kg isotope data relates to the concentration of stable calcium in the exchangeable pool, of which the serum calcium is a measure. Quantitation of bone-formation and resorption rates are best expressed, therefore, as absolute units of calcium, corrected for body size. The normal ranges were obtained in ten normal subjects.¹⁸ The exchangeable calcium pool (Ca_E) was considerably decreased to 32 mg calcium/kg or 8.0 plasma units. The rate of uptake of isotope into bone, expressed as a percentage of the exchangeable pool, was at the lower limit of normal; bone-formation rate was low, being 3.6 mg calcium/kg body weight (mean normal \pm 2SD = 6.4 ± 1.8 mg/kg).

Bone-resorption rate cannot be measured directly. By definition, bone-resorption rate equals bone-formation rate minus balance. Calcium balance data in our patient are not yet complete. Preliminary figures, however, not yet corrected for fecal chromium excretion, show a highly positive calcium balance. This finding, in conjunction with a low bone-formation rate suggests that the bone-resorption rate in this case must be extremely low.

Calcium infusion: Before infusion, serum calcium was 7.6 mg/100 ml. At the end of the infusion, serum calcium had risen by 2.7 mg/100 ml but the maximum increment of 3.4 mg/100 ml was not reached until the tenth hour after the start of the infusion (Fig. 2). Thereafter this maximum level of serum calcium (11.0 mg/100 ml) was maintained unchanged 12 and 24 hours after the start of the infusion.

TABLE 2. Summary of serum and isotope data from patient with medullary carcinoma of the thyroid.

Subjects	Serum ^a				
	Calcium (mg/100 ml)	Phosphate (mg/100 ml)	Alkaline phosphatase (Bod. U.)		
Normals	9-11	3.0-4.5	1-4		
Patient (wt. 73 kg)	6.0-9.0	2.2-4.3	4.6-12		
	Calcium Kinetics ^b				
	Ca _E ^c		C _B		E.F.C. ^d
	(Plasma U)	(mg/kg)	(Plasma U)	(mg/kg/day)	(mg/day)
Normals	13.4 ± 5.1	68 ± 13.3	1.2 ± 0.4	6.4 ± 1.8	136 ± 58
Patient (wt. 73 kg)	8.0	32.0	0.9	3.6	92

^a Values given are ranges.

^b Values given are means \pm 2 standard deviations.

^c Ca_E = Exchangeable calcium pool; C_B = uptake of isotope into bone, or bone-formation rate.

^d E.F.C. = endogenous fecal calcium.

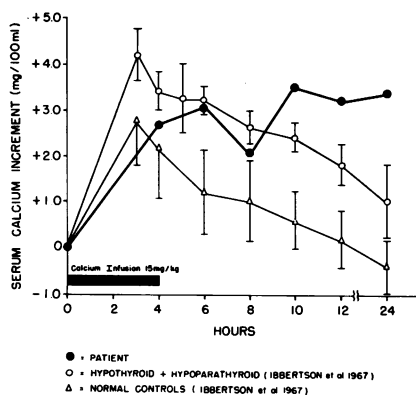


FIG. 2.—Serum calcium increments after calcium infusion in a patient with medullary carcinoma of the thyroid. Shown also, for comparison, are results (mean \pm 1 SD) from 3-hr infusions (12 mg/kg) in nine normal controls, and four thyroparathyroidectomized patients, published by Ibbertson *et al.*²⁵ The latter group of four patients resembled our own patient insofar as they were hypocalcemic and receiving both calciferol and thyroid-replacement therapy.

Discussion.—The clinical picture in any endocrine-excess syndrome depends upon the physiological action of the secreted hormone and the compensatory mechanisms involved in response to this action. The known effects of thyrocalcitonin are hypocalcemia, hypophosphatemia, and inhibition of bone resorption. The primary compensatory reaction to hypocalcemia is stimulation of parathyroid hormone secretion. The present case appears to be the first documented example of excessive secretion of thyrocalcitonin, and the term “hyperthyrocalcitoninism” would seem appropriate to describe the syndrome.

The patient was severely hypocalcemic despite treatment with 100,000 units of vitamin D daily. Later, following an increase of vitamin D to 200,000 U/day, his plasma calcium gradually rose to 9.0 mg/100 ml. Plasma phosphate was also low, rising later on treatment. He was found to have extensive metastatic medullary carcinoma of the thyroid which contained 1000–2000 times more thyrocalcitonin per unit weight than normal thyroid tissue. High concentrations of thyrocalcitonin were measured also in the plasma. We presume that the tumor was the source of the circulating thyrocalcitonin, and that this in turn led to hypocalcemia and hypophosphatemia. It was considered unlikely that the tumor was sequestering thyrocalcitonin from the plasma, rather than synthesizing it, since the patient had little or no normal thyroid tissue remaining. The presence of hypocalcemic activity in plasma after excision of the pheochromocytomas rules out the possibility that thyrocalcitonin was produced by these. Other causes of hypocalcemia were unlikely. The patient was not hypoparathyroid, as shown by high circulating levels of parathyroid hormone. Although the patient suffered from diarrhea, this was not severe and there was no steatorrhea. In addition, the high urinary calcium, the long-term treatment with high doses of vitamin D and calcium, and low bone-turnover rate make osteomalacia unlikely.

Although bone density was not measured quantitatively, it did not appear to be radiologically abnormal. In view of the effect of thyrocalcitonin in inhibiting bone resorption, it might be expected that an excess of this hormone would result in an increased bone density. Since in our patient the bone-formation rate was also diminished, it is possible that the net disparity between accretion and resorption was small and that insufficient time had elapsed for this to become apparent radiologically.

Isotopic studies of bone turnover showed this to be low in accordance with the inhibitory action of thyrocalcitonin on bone resorption. It is of interest that in this patient a low rate of bone turnover was maintained in spite of increased circulating parathyroid hormone. The absence in this case of bone changes—both radiological and kinetic—of hyperparathyroidism may be explained by the diminished effectiveness of parathyroid hormone in the presence of excessive thyrocalcitonin.²⁴ Measurement of bone resorption, however, is presently unsatisfactory, being subject to the combined errors of both balance and isotopic techniques. Nevertheless, measurements in this case suggest that bone resorption was decreased. Additional support for this lies in the absence of the usual “break” or change in the slope of the serum and urine specific-activity lines over the 14 days of the isotope study.

The handling of an infused calcium load is inefficient in the absence of functioning thyroid tissue,²⁵⁻²⁸ and this is considered to reflect a deficiency of thyrocalcitonin release in response to the induced elevation of serum calcium. The failure in our case of the serum calcium to fall for 24 hours after the infusion is unusual. This may be explained by assuming that in the presence of excessive thyrocalcitonin, any increase in the secretion of this hormone in response to an induced rise in plasma calcium would be ineffective in further reducing bone resorption that is already suppressed maximally. A low bone-turnover rate and diminished pool size would further contribute to a slow return to resting levels of an induced hypercalcemia.

On two occasions, it was noted that the plasma level of thyrocalcitonin appeared to be related to the plasma calcium concentration. Plasma thyrocalcitonin was higher postoperatively when the serum calcium had risen to 7.1 mg/100 ml than preoperatively when it was 6.0–6.5 mg/100 ml. In another pair of plasma samples, thyrocalcitonin was higher following a calcium infusion than it was before the infusion (Table 1). It is presumed that despite high basal secretion, even in the presence of hypocalcemia, the tumor responded to a rise in plasma calcium by increasing still further its secretion of thyrocalcitonin.

The findings in this case strongly support the observations by Williams¹¹ on the histogenesis of medullary carcinoma of the thyroid. On the basis of histological similarities between human medullary carcinoma and parafollicular cell tumors in rats and dogs, he postulated that the tumor arose from similar cells in the human thyroid. If this is so, this case offers proof hitherto lacking that the parafollicular cell in the human is—as in other species—the site of origin of thyrocalcitonin.

Summary.—A patient is described who presented with medullary carcinoma of the thyroid and tetany. He was shown to be hypocalcemic and hypophosphatemic. Remarkably high concentrations of thyrocalcitonin were demonstrated in the tumor tissue and in the plasma, together with high levels of circulating parathyroid hormone. Radiocalcium studies showed diminished exchangeable calcium and bone turnover. The intravenous infusion of calcium produced an elevation of serum calcium that was slow to return to resting levels and which was accompanied by a further increase in plasma thyrocalcitonin concentration.

The term "hyperthyrocalcitoninism" is suggested as appropriately describing this syndrome.

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